REMARKS

Claims 1-23 are currently pending in the application. Claims 1-5 are amended. The amendments find support in the specification and are discussed in the relevant sections below. No new matter is added.

Rejection of Claims 1 and 3 Under 35 U.S.C. §102(b)

The Examiner has rejected claims 1 and 3 under 35 U.S.C. §102(b) as allegedly anticipated by Cliffe et al. The Examiner asserts that Cliffe et al. report combinations of DMXAA and alkylating agents such as SN23862 or SR4233.

Applicants submit that claims 1 and 3 are amended herein to specifically recite "cyclophosphamide", and are no longer drawn to the genus of alkylating agents. Support for this amendment is found at page 9, line 11. Cliffe et al. do not teach a combination of DMXAA and cyclophosphamide and, therefore, do not anticipate the claimed invention. Applicants respectfully request that the rejection be reconsidered and withdrawn.

Rejection of Claims 1-23 Under 35 U.S.C. §103(a)

Siemann et al.

The Examiner has rejected claims 1-23 under 35 U.S.C. §103(a) as allegedly being obvious over Siemann et al. The Examiner asserts that Siemann et al. teach methods of treating sarcoma, breast, and ovarian tumors with a combination of DMXAA and cisplatin or cyclophosphamide. The Examiner asserts that Siemann et al. teach that when DMXAA is combined with these conventional chemotherapeutics, tumor cell kill was increased 10-500 fold compared to that seen with chemotherapy alone. The Examiner concludes that, although Siemann et al do not teach administration of DMXAA combinations to mammals, or specific compositions or pharmaceutical compositions comprising DMXAA combinations, that it would be obvious to modify Siemann et al in this way because "one would reasonably expect" the combinations to work *in vivo* in a mammal, and "one would reasonably expect" the compositions, kits, or pharmaceutical compositions to be useful. Applicants respectfully

disagree with the Examiner, and submit that the Examiner has not established a *prima facie* case for obviousness.

To establish a *prima facie* case of obviousness, several criteria must be met, the most pertinent of which is that there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings (*In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)). Applicants submit that there is no motivation to modify the teachings of Siemann et al. to arrive at the claimed invention.

Methods of treatment (claims 1-6)

Applicants submit that Siemann et al. provide insufficient disclosure to motivate one of skill in the art to modify the experiments reported therein to arrive at the claimed method for treating cancer in a mammal. Siemann et al. report ***in vitro*** data, in which combinations of either DMXAA, or a second vascular targeting agent, CA4DP, and a "a range of doses" of cisplatin or cyclophosphamide were shown to increase tumor cell kill by 10-500 fold compared to chemotherapy alone. Siemann et al do not report what concentrations of cisplatin or cyclophosphamide were used, and do not even report what "range of doses" was used. In addition, Siemann et al. do not teach which of the at least four possible combinations of drugs (DMXAA + cisplatin; DMXAA + cyclophosphamide; CA4DP + cisplatin; CA4DP + cyclophosphamide) produced the increased tumor cell killing and, further, do not teach or suggest which of the four combinations of drugs worked better or worse than the others. Because there is no teaching relating to dosing, or which particular combination of compounds was effective in increasing tumor kill, one of skill in the art would not reasonably conclude that Siemann et al. had used physiologically relevant doses which would permit the treatment of cancer in a mammal and, thus, would not reasonably conclude that the studies reported by Siemann et al. could be extrapolated to an *in vivo* treatment method. In addition, the assay reported by Siemann et al. measures the survival of only a small proportion of the cells within the tumor a short time after exposure to the drugs. Siemann et al do not report on the effect of the combinations on tumor vascular endothelial cells, which are the target of DMXAA, nor does

Siemann et al. address the question of repopulation of tumor cells following the initial therapy. Thus, there is no teaching in Siemann et al., that would suggest to one of skill in the art that the combinations reported would be an effective treatment *in vivo*.

Given that Siemann et al. only report on *in vitro* studies, that they do not provide any teachings relating to the concentrations of cisplatin or cyclophosphamide which were used, and that they do not report whether it was either of the combinations of DMXAA and cisplatin or DMXAA and cyclophosphamide which produced the large increase in cell killing, it would not be obvious to one of skill in the art that the results would extrapolate to the same cytotoxic effect in solid tumors *in vivo* (i.e., in a method for treating cancer in a mammal). In fact, in a paper published by Siemann et al following the poster abstract (Siemann et al. 2002, Int. J. Cancer 99:1-6; Exhibit A), the authors conclude that a "small therapeutic window [for DMXAA] may be a major drawback to the clinical potential of DMXAA" (see, Discussion, p. 5). One of skill in the art would not have been motivated, based on the teachings of Siemann et al. to utilize the specific combinations of DMXAA and cisplatin or cyclophosphamide in a method for treating cancer in a mammal.

Obvious to try

Due to the complete absence of any disclosure relating to modification of the reported *in vitro* studies to achieve an *in vivo* method for treating cancer in a mammal, the experiments described by Siemann et al, at best, renders the present invention obvious to try. The Federal Circuit has long held that "obvious to try" does not constitute "obviousness." The court in *In re O'Farrell* (853 F.2d 894, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988)) made an excellent distinction between these two concepts. Judge Rich noted that "[a]ny invention that would in fact have been obvious under §103 would also have been, in a sense, obvious to try. The question is: when is an invention that was obvious to try nevertheless nonobvious?" (*Id.* at pages 1680-81). He went on to state that

> The admonition that 'obvious to try' is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior

> art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. *[4 case cites omitted]*. In others, what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

(*Id.*, at 1681). Given the scarce disclosure found in Siemann et al., the Examiner's rejection under §103 falls clearly into Judge Rich's first category. The disclosure in Siemann et al. may, at most, suggest to one of skill in the art to try out the infinite possible dosages of cisplatin or cyclophosphamide (infinite because Siemann et al. do not even suggest an upper or lower limit of possible dosages) in combination with either DMXAA or CA4DP in an *in vivo* cancer setting to see if they would work in a manner similar to the *in vitro* studies reported by Siemann et al. This does not rise to the level of obviousness. Applicants therefore submit that the present invention is not obvious over the teachings of Siemann et al., because Siemann et al. do not provide the requisite motivation to administer combinations of DMXAA and cisplatin or cyclophosphamide to a mammal to treat cancer.

The Examiner asserts further that, with respect to claims 2 and 3 (drawn to administering the compounds in a potentiating ratio or concomitantly), it would be obvious to one of skill in the art to administer the two compounds in such a manner as to optimize the therapeutic efficacy. Based on the same rationale as asserted above, Applicants respectfully disagree. As noted above, one of skill in the art would not have been motivated, based on the teachings of Siemann et al., to utilize combinations of DMXAA and cisplatin or cyclophosphamide in mammalian cancer treatment. It would also, therefore, be nonobvious to administer the compounds either concomitantly or in a potentiating ratio. Since there is no information given as the dosages of cisplatin or cyclophosphamide used, one of skill in the art would not know or reasonably discover a potentiating ratio of compounds.

Compositions, kits, and pharmaceutical formulations (Claims 7-23)

The Examiner asserts that the disclosure provided by Siemann et al. would also render obvious the claims of the instant invention drawn to compositions comprising DMXAA combinations, kits comprising DMXAA combinations, and pharmaceutical formulations

comprising DMXAA combinations. Applicants respectfully disagree. Again, Siemann et al. fail to teach or even suggest that the *in vitro* data they report could be reproduced *in vivo*, and provide no indication of dosage or routes of administration which could be used to carry out treatment using a specific combination of DMXAA and cisplatin or cyclophosphamide. Moreover, Siemann et al. do not even report that it was the specific combinations of DMXAA and cisplatin or cyclophosphamide which achieved the large increase in tumor cell killing *in vitro*. Accordingly, one of skill in the art would not have been motivated to include DMXAA and cisplatin or cyclophosphamide in compositions, kits, or pharmaceutical formulations for treatment because there is no reasonable expectation which can be derived from Siemann et al. that the specific combinations of DMXAA and cisplatin or cyclophosphamide are useful for treating cancer. In other words, because one of skill in the art would not be motivated to extrapolate the teachings of Siemann et al., to mammalian cancer treatment, one of skill in the art would be similarly unmotivated to incorporate the combination into kits, or pharmaceutical formulations.

Applicants submit that the instant invention is novel and non-obvious over Siemann et al. and respectfully request that the Examiner's rejection be reconsidered and withdrawn.

Wilson; Siemann et al.; Zhou et al.

The Examiner has rejected claims 1-23 under 35 U.S.C. §103 as being obvious over Wilson in view of Siemann et al., or Zhou et al. Applicants respectfully disagree.

Applicants submit that the present invention and the Wilson reference were, at the time the invention of the present application was made, commonly owned or subject to an obligation of assignment to Auckland UniServices Limited. Accordingly, because Wilson is prior art against the instant application under 35 U.S.C. §102(e), the provisions of 35 U.S.C. 103(c) permit Applicants to remove this reference as prior art against the instant claims.

Absent the Wilson reference, the Examiner's rejection is restricted to the combined teachings of Siemann et al. and Zhou et al. As described above, Siemann et al. does not render the present invention obvious. Zhou et al. reports that the anti-cancer agents vincristine,

vinblastine, amsacrine, and daunorubicin do not have a predicted inhibitory effect on DMXAA metabolism. Siemann et al. does not teach or suggest combination of DMXAA with any other anti-cancer agent (nor does Siemann et al. actually report on the desirability of the combination of DMXAA and cisplatin or cyclophosphamide), and thus, provides no motivation to combine DMXAA with any of the anti-cancer drugs reported on by Zhou et al. Likewise, Zhou et al. merely makes predictions about the *in vitro* pharmacokinetics of certain anti-cancer drugs on DMXAA metabolism, and indicates that the predicted interaction "does not rule out the possibility of pharmacokinetic interactions with other drugs." Zhou et al. do not address the efficacy of any of the chemotherapeutic agents studied, nor whether these metabolic effects are replicated *in vivo*. In addition, it is not the case that metabolic interaction observed using *in vitro* systems would lead predictably to increased efficacy of the combination of DMXAA with any other anticancer drugs. For example, Cliffe et al. (cited by the Examiner) reported enhanced anti-tumor effect of a combination of DMXAA and tirapazamine, while Zhou et al. report that tirapazamine has no effect on the metabolism of DMXAA. Clearly, there is no correlation between the metabolism and efficacy studies of anti-cancer drug combinations and, therefore, it would not be obvious that the results published by Zhou et al. would suggest to one of skill in the art an increased antitumor effect by combining DMXAA with conventional chemotherapy agents (e.g., cisplatin or cyclophosphamide) in solid tumors *in vivo*. Taken together, the combined teachings of Siemann et al. and Zhou et al. fail to teach or even intimate at the feasibility or desirability of combining DMXAA with anti-cancer compounds as claimed in the instant invention for treatment of cancer in a mammal. Applicants submit, therefore, that Siemann et al. and Zhou et al., alone or in combination, do not render the present invention obvious, and respectfully request that the rejection be reconsidered and withdrawn.

Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

Respectfully submitted,

Date: May 10, 2005

Name: Matthew Beaudet
Registration No.: 50,649
Customer No.: 29933
Palmer & Dodge LLP
111 Huntington Avenue
Boston, MA 02199-7613
Tel. (617) 239-0100